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10/550,671	11/09/2005	Hideaki Yamaoka	TOYA114.007APC	1379

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/550,671	YAMAOKA ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 10 October 2008.

Claim Status

Claims 1-6 and 8-9 are pending. Claim 1 is amended. Claim 7 is canceled. Claims 1-6 and 8-9 are under current examination.

Priority

This application claims benefit as a 371 of PCT/JP04/04074 (filed 03/24/2004). This application claims benefit from foreign application JAPAN 2003-082739 (filed 03/25/2003). The examiner was in error in his previous action in asserting that the application was not entitled to a benefit date, based on the foreign application, JAPAN 2003-082739. The examiner has reassessed the claim to benefit. Accordingly, the instant application has been granted the benefit date, 25 March 2003, from JAPAN 2003-082739.

RESPONSE TO ARGUMENTS

Response to Arguments – 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-6 and 8-9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sode (WO/2002/36779, published 10 May 2002) in view of Herbaud et al. (Biochim. Biophys Acta. 2000; Vol.1481(1): 18-24) as evidenced by Arslan et al. (Biochem. Biophys. Res. Commun. 251 (1998) 744-747) for the reasons of record and the comments below.

Applicant's arguments and claim amendments filed 10 October 2008 have been fully considered but they are not persuasive.

The applicant has amended instant claim 1 to recite "improving expression of glucose dehydrogenase and providing high glucose dehydrogenase activity." The applicant also indicates support for this language in the specification (page 2, last full paragraph). The applicant asserts, “one of ordinary skill in the art would understand that ‘improved’ and ‘high’ mean by comparison to wild strain or a recombinant bacteria which do not ‘comprise genes of a ccm operon operably linked to a promoter’ as claimed (*Burkhorderia cepiacia* KS1 and JM109/pTrc99Aγαβ, present specification,

page 20)" (Remarks, page 4, lines 4-7). The examiner finds the applicant's arguments unpersuasive. The applicant has not claimed *Burkhorderia cepiacia* KS1 and JM109/pTrc99Aγαβ. Additionally, the claims do not recite "comparison to wild strain or a recombinant bacteria which do not 'comprise genes of a ccm operon operably linked to a promoter.'" As discussed in the new grounds 35 USC 112-2nd paragraph rejection below, the examiner believes the claim amendments have introduced more "relative terms" into the instant claims. Consequently, the examiner finds this argument unpersuasive

The applicant further argues that "the discovery that the ccm system improved expression and provided high activity of GDH was not expected." (page 4, lines 15-16). The applicant states that the basis for the statement "the cited art indicates that maturation of cytochrome C was increased in *E.coli* when co-expressed with the ccm genes" is not clear, but fails to explain what is not clear. Herbaud et al. teach "that when the ccm genes are provided on a plasmid together with the structural gene for a mono- and a diheme c-type cytochrome, the cytochrome maturation occurs and seems to be increased" (page 18, col.2). The examiner cited Herbaud et al to satisfy the claim limitations. The examiner does not need to explain why Herbaud came to the same conclusion as the inventors that co-expression of ccm with GDH causes improved expression, while Sode et al. teach that their GDH had activity. Since the instant claims recite relative term "high," the examiner interprets the teachings of Herbaud and Sode as satisfying the instant claims.

The applicant also argues there is no motivation to combine the cited art (Remarks, page 5, line 5). The examiner had included a motivation to combine the teachings in the Action, filed 6/1/2008: The person of ordinary skill in the art would have been motivated to modify the teachings of Sode in with the teachings of Herbaud et al. because "when the ccm genes are provided on a plasmid together with the structural gene for a mono- and a diheme c-type cytochrome, the cytochrome maturation occurs and seems to be increased" (Herbaud et al., page 18, col.2).

The applicant also argues that unexpected results were obtained with the claimed combination compared to the prior art. Specifically, the applicants demonstrated the GDH activity of ccm system in E.coli was 23-fold higher than in *Burkhorderia cepiacia* KS1 strain. The applicant argues that such high expression levels could not have been predicted from the cited references. The examiner finds this an interesting argument. The structure of the claimed bacterium is suggested by the prior art and the examiner has made the prima facie case. MPEP 2111.04 states "Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure." In the instant case, the examiner believes that the portion of claim 1 following the word, "thereby," does not limit the particular structure of the claimed *E. coli* bacterium. Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant argues the cited art does not teach or suggest that expression of a ccm system in E.coli has any effect on a glucose dehydrogenase (or other enzyme) activity." (Remarks, page 6, lines 1-4). The cited art indicates that maturation of cytochrome C (i.e., α-subunit and the β-subunit of glucose dehydrogenase) was increased in *E.coli* when co-expressed with the ccm genes (Herbaud, page 18, col.2) and further teaches that as a result, "[t]he production of cytochrome c_3 (M_r 13,000) was increased by about 10%" (Herbaud, page 21, col.2, lines 3-5). The claims do not indicate the meaning of a "high GDH activity." Therefore, the examiner finds that the teachings of the cited art are sufficient to satisfy the instant claims. Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant points to an embodiment of Arslan et al. to cast doubt on the predictability of the combination of the cited art (Remarks, page 6, lines 9-12). However, this embodiment was grown without pEC86 (contrary to the limitations required by claim 8). Therefore, the examiner finds this embodiment irrelevant invention suggested by combination of references which includes plasmid. pEC86. Accordingly, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1-6 and 8-9 under 35 USC 103(a) as obvious over Sode in view of Herbaud et al. and as evidenced by Arslan et al.

The examiner repeats the rejection of record (Action, filed 6/1/2007) below:

Claims 1-6 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sode (WO/2002/36779, published 10 May 2002) in view of Herbaud et al.

(Biochim. Biophys Acta. 2000; Vol.1481(1): 18-24) as evidenced by Arslan et al. (Biochem. Biophys. Res. Commun. 251 (1998) 744-747).

Claim 1 is directed to an *Escherichia* bacterium, comprising DNAs encoding the α-subunit and the β-subunit of glucose dehydrogenase of *Burkhorderia cepiacia* in an expressible form and further comprising genes of a ccm Operon operably linked to a promoter, thereby enhancing the expression of a cytochrome c maturation (ccm) system and glucose dehydrogenase. Sode et al. teach DNA encoding α-subunit, β-subunit, and γ-subunit (WO/2002/36779 Translation, lines 512-513, 592-595 and 722-724) of glucose dehydrogenase of *Burkhorderia cepiacia* (Translation, lines 530-531). Sode teaches, plasmids including pBR322, pUC18, and pUC19 are suitable for expression of glucose dehydrogenase subunit genes in the host bacteria, *Escherichia coli* (Translation, lines 623-624). Intrinsically, Sode teaches constitutive expression of the glucose dehydrogenase, as suggested by the ability of Sode to produce the glucose dehydrogenase complex by merely culturing the transformed bacteria (Translation, lines 20-23). There is no mention of inducible promoters, so the examiner interprets the Sode reference as having constitutive expression of the glucose dehydrogenase subunits. According to the instant specification, the phrase “enhance the expression of the ccm system” is defined to mean recombinant glucose dehydrogenase genes constitutively expressed in *Escherichia* (Specification, page 9, parag.2).

Claim 2 is directed to the Escherichia bacterium according to claim 1, wherein the DNA encoding the α-subunit is located upstream from the DNA encoding the β-subunit, and expression of the subunits is regulated by a single promoter. Sode

teaches, expression plasmids comprising nucleic acid sequences wherein the alpha subunit is upstream of the beta subunit (lines 723-724).

Claims 3-4 are directed to the Escherichia bacterium according to claim 1, wherein the DNA encoding the γ-subunit is located upstream from the DNA encoding the α-subunit. Sode teaches, transformants comprising expression plasmids wherein the nucleic acid sequence for the gamma subunit is upstream of the alpha subunit (lines 1230-1233).

Claim 5 is directed to the Escherichia bacterium according to claim 1, wherein the Escherichia bacterium is Escherichia coli. Sode teaches transformation of E. coli with the plasmids comprising α-subunit, β-subunit, and γ-subunit of GDH.

Claim 6 is directed to a method for producing a glucose dehydrogenase complex, which comprises culturing the *Escherichia* bacterium according to claim 1 so that the DNAs encoding the α-subunit and the β-subunit are expressed and the glucose dehydrogenase complex is produced, and collecting the complex. Sode teaches, "The manufacture procedure of the glucose dehydrogenase characterized by belonging to *Burkhorderia cepiacia*, cultivating to a medium the microbe which has the capability to produce glucose dehydrogenase, and extracting glucose dehydrogenase from this medium or/and said microbe cell." (Translation, lines 20-23).

Claim 8 is directed to the Escherichia bacterium according to claim 7, wherein the plasmid is pEC86.

Sode. does not teach the specific plasmid, pEC86.

Herbaud et al. teach E. coli transformed with "pEC86 that contains the ccm genes" (page 19, col.2), in particular, those encoding α-subunit, β-subunit, and γ-subunit. Herbaud also teach "when the ccm genes are provided on a plasmid together with the structural gene for a mono- and a diheme c-type cytochrome, the cytochrome maturation occurs and seems to be increased" (page 18, col.2).

Claim 9 is directed to the Escherichia bacterium according to claim 1, wherein the bacterium is modified so that the expression of the ccm system is enhanced by replacing the bacterium's ccm operon promoter with another promoter. Herbaud teaches the plasmid, pEC86. Herbaud et al. (page 19, Materials and Methods, section 2.1) indicate that Arslan et al. describe in greater detail the structure of pEC86. Arslan et al. teach, "Overproduction of c-type cytochromes with pEC86 encoding the *ccm* genes." (page 745, col.1, Results). Arslan et al. further teach, "Plasmid pEC86 is derived from the vector pACYC184 and contains the *ccm* genes downstream of the *tet* promoter." (page 745, col.2). In addition, Arslan et al. teach, "Plasmid pEC86 provides a tool for constitutive *ccm* gene expression and in particular facilitates aerobic cytochrome *c* maturation. It can also be used to increase the amounts of endogenous *c*-type cytochromes." (page 747, col.1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to utilize the specific plasmid, pEC86, as taught by Herbaud et al. with the invention of Sode.

The person of ordinary skill in the art would have been motivated to modify the teachings of Sode in with the teachings of Herbaud et al. because "when the ccm genes

are provided on a plasmid together with the structural gene for a mono- and a diheme c-type cytochrome, the cytochrome maturation occurs and seems to be increased" (Herbaud et al., page 18, col.2).

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Sode and Herbaud et al. because each of these teachings generated enhancement of the ccm system.

Therefore the method as taught by Sode in view of Herbaud et al. and as evidenced by Arslan et al. would have been *prima facie* obvious over the method of the instant application.

Therefore, the examiner hereby maintains the rejection of claims 1-6 and 8-9 under 35 USC 103(a) as obvious over Sode in view of Herbaud et al. and as evidenced by Arslan et al.

Claim Rejections - 35 USC § 112

The rejection of claims 1-6 and 8-9 are rejected under 35 U.S.C. 112, first paragraph (new matter) is withdrawn in response to the applicant's arguments and/or claim amendments.

The applicant's arguments have been fully considered and are persuasive.

Therefore, the examiner hereby withdraws the rejection of claims 1-6 and 8-9 under 35 USC 112, 1st paragraph (new matter).

35 U.S.C. 112, second paragraph

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 8-9 remain under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant has argued that inclusion of phrases such as “abundantly expressing” and “extremely high GDH activity” in the specification is sufficient to overcome the instant rejection. However, these terms "abundantly" and “extremely" are themselves relative terms and indefinite. Therefore, the examiner finds the applicant’s arguments unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1-6 and 8-9 under 35 USC 112, 2nd paragraph.

The examiner reiterates the pending rejection

The phrase "enhancing the expression of…glucose dehydrogenase" in claim 1 is a relative term which renders the claim indefinite. The term "enhancing the expression of…glucose dehydrogenase" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The specification does not specifically mention “enhancing expression of glucose dehydrogenase.” The specification indicates “‘expression of the ccm system is

enhanced' means that the expression is enhanced compared with that in a wild strain or unmodified strain of Escherichia bacteria" (page 9, lines 2-5). The specification also states, "[a]ccording to the present invention, an enzyme complex containing the α-subunit and the β-subunit of glucose dehydrogenase of *Burkhorderia cepiacia* can be abundantly expressed in *Escherichia* bacterium (last lines of page 20 bridging page 21). The specification does not make clear whether the "abundantly expressed GDH" is actually "enhanced compared to wild strains" in a similar way as is defined for expression of the ccm system. Without an explicit definition for "enhanced expression of GDH," it is indefinite as to what the level of glucose dehydrogenase is being compared.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 8-9 are under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "improving expression of glucose dehydrogenase and providing high glucose dehydrogenase activity" in claim 1 contains relative terms which renders the claim indefinite. The term "improving" is not defined by the claim, the specification does

not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Furthermore, the term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The specification does not specifically define “improving expression of glucose dehydrogenase.” The specification indicates “expression of a DNA encoding a glucose dehydrogenase complex of *Burkhorderia cepacia* could be improved in an Escherichia bacterium by enhancing the expression of the ccm system of the bacterium, and thus accomplished the present invention” (page 2, lines 28-32). However, this statement does not clearly indicate what is meant by “improving expression.” Therefore, the claim contains indefiniteness about the level of expression.

Also, the specification does not specifically define “high glucose dehydrogenase activity.” The specification states, “JM109/pTrc99AγαβpBBJMccm exhibited an extremely high GDH activity.” (page 20, lines). However, this statement does not clearly indicate what is meant by “high glucose dehydrogenase activity.” Therefore, the claim contains indefiniteness about the level of glucose dehydrogenase activity.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner, Art Unit 1633

/Janet L. Epps-Ford/
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